CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022472Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **COMPLETE RESPONSE**

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your New Drug Application (NDA) dated and received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We acknowledge receipt of your amendments dated June 29, July 27, August 6 and 27, September 24, November 5, 15, and 24 (2), and December 14 (2), 2010.

The June 29, 2010, submission constituted a Complete Response to our March 12, 2010, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. In your original NDA submission, you proposed to market Afrezza with a MedTone inhaler and cartridges that contain 15 units or 30 units of drug product. You are now proposing to market Afrezza using a new Gen2 inhaler with re-designed cartridges that contain 10 units or 20 units of drug product. However, there are no controlled phase 3 clinical trial data with the Gen2 device to support its efficacy and safety. Instead, you are attempting to rely on *in vitro* performance data and a clinical pharmacology bridge to the phase 3 trials conducted with the MedTone inhaler. This approach is inadequate because we cannot be assured that the Gen2 device will be a safe and effective product based on these limited data. Because the Gen2 device has not been studied in controlled phase 3 clinical trials, meaningful information regarding patient use and device robustness and their impact on efficacy and safety is lacking.

   Therefore, you should conduct two randomized, controlled phase 3 trials with the Gen2 device, one in patients with type 1 diabetes and the other in patients with type 2 diabetes.

At least one of these trials should include a treatment group using the MedTone C inhaler so that we can obtain a head-to-head comparison of the pulmonary safety data for the two devices. These trials should be of sufficient duration to permit an adequate titration of study medication and there should be at least twelve weeks of relatively stable insulin doses at the end of the treatment period so that the endpoint HbA1c adequately reflects preceding glycemic control.

Inadequate titration of insulin doses has been an important limitation of all phase 3 clinical trials conducted with the MedTone inhaler to date. Therefore, your phase 3 trials with the Gen2 inhaler should ensure that appropriate titration of insulin doses occurs. Strategies include use of a titration algorithm, investigator training with frequent reminders about titrating insulin doses, and review of glucose data while the trials are ongoing with feedback to investigators when there is evidence of inadequate titration.

Adverse events of interest in the Gen2 phase 3 trials should include pulmonary safety (with pulmonary function testing), hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events (given that there were numerically more cases of retinal detachment with Afrezza vs. comparator in the controlled phase 2/3 MedTone program), and device-related performance issues. We strongly encourage you to submit the protocols for these studies for review prior to implementation.

2. Submit updated analyses of lung cancer cases in the Afrezza program. These analyses should include adjustments for patient-year exposure and should compare the rates of lung cancer among Afrezza-treated patients to the background rates among smokers and non-smokers.

CLINICAL PHARMACOLOGY

3. Clinical site and analytical inspection results are not yet available for your clinical pharmacology study (MKC-TI-142) comparing the Medtone C inhaler to the Gen2 inhaler. These inspection results must be acceptable if this study is needed in your resubmission to support approvability of the Gen2 device.

PRODUCT QUALITY

4. Conduct a study of the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges under the following conditions of use: low temperature and low humidity. The purpose of this study is to evaluate whether the performance characteristics of the 10 unit dosage strength cartridges are affected by static on the contact surfaces of the inhaler under these temperature and humidity conditions.

5. Conduct a study evaluating the impact of potential issues during shipment, such as settlement or leakage, on the emitted dose and aerodynamic particle size distribution attributes of the Gen2 10 unit dosage strength cartridges.

6. Conduct a study of Gen2 inhalers evaluating emitted dose and aerodynamic particle size distribution attributes under misuse scenarios (e.g., dropping, shaking).

7. Conduct a study of the insulin adduct impurities and insulin-related degradants in support of the limits on these compounds as proposed in the November 24, 2010 amendment to the NDA. Submit adequate supporting data, including a validated method for monitoring insulin-FDKP adducts on stability.

DEVICE

8. Revise the storage conditions for the Gen2 inhaler to reflect the actual test conditions of (b) (4) degrees Celsius.

9. Complete mouthpiece retention testing after shelf-life and simulated use conditions in your stability testings. The purpose of this test is to evaluate whether (b) (4)

Human Factors

10. You have proposed changes to the Instructions for Use (IFU) and cartridge strength label based on patient use errors identified in your completed usability study. Perform a new usability study to demonstrate that these changes minimize the previously identified user errors without introducing new risks. We strongly encourage you to submit the protocol for review prior to implementation of the study. This study should test representative device users, with the final design of the Gen2 inhaler and IFU. This study should also test for possible dosing errors resulting from confusion between the labeled drug content of the cartridges (10 units or 20 units) and the deliverable insulin dose (equivalent to ~4 or 8 units of subcutaneous insulin).

11. Your usability study did not test whether patients can correctly calculate dosing of insulin when converting from subcutaneous prandial insulin to Afrezza and vice versa. Because patients may need to sometimes switch from Afrezza to subcutaneous insulin (e.g., on sick days) or from subcutaneous insulin to Afrezza (e.g., upon initiating Afrezza, after sick days have resolved), your new usability study should test whether patients can accurately convert between inhaled and subcutaneous insulin doses. If insulin dose conversion charts are needed in product labeling, you should test that patients can adequately use these charts.

12. You state that referring to the IFU will mitigate many of the user errors identified in the completed usability study. However, many of these errors occurred because the users did not recognize or were not aware of the IFU. Therefore, your follow-up usability study should demonstrate that reference to the IFU in its final version is an effective risk mitigation strategy.

13. Provide a detailed description of the user training program you propose for your marketed product. Include clarifications with rationale as to whether all patients who are prescribed Afrezza will be trained. If training will not be consistently provided to prescribed users, provide an estimate of the likely proportion of untrained users to the entire user population, and reflect this proportion in your usability study to ensure that your study includes the expected untrained user population.

LABELING

14. Include the statement required by 21 CFR 801.109 for prescription devices: "Caution: Federal law restricts this device to sale by or on the order of a physician."

When you submit your Complete Response, address the following labeling comments to help mitigate the risk of errors resulting from errors in wrong technique and dosing.

All Carton, Foil Wrap, and Blister Pack, and Device Labeling

15. Delete the name [redacted] from all labeling and the device as you withdrew the name [redacted]" on August 27, 2010.

Cartridge Blister Pack Label

16. Both strengths for Afrezza Inhalation Powder printed on the blister label employ [redacted] background color; thus, increasing the similarity between the two strengths, which can lead to selection and dosing errors. Revise the background color consistent with other labeling for the product: use the blue color for the 10 unit strength and the green color for the 20 unit strength.

17. The labeled strength does not match the inhaled insulin dose. We recommend an additional statement immediately underneath the strength "delivers approximately X units of subcutaneous insulin."

Cartridge Foil Wrap Labeling

18. Revise the phrase [redacted] to state "delivers approximately". As currently presented, the word [redacted] is misleading. It implies that the [redacted].

19. Revise the statement located on the principal display panel in storage information "Cartridge must be at room temperature before use" to define the amount of time the cartridge must be stored at room temperature prior to use.

20. Increase the prominence of the statement "Inhale once and then discard cartridge immediately" by increasing the font size and using bold font. We recommend this change to emphasize that the cartridge should be discarded immediately after being removed from the inhaler to avoid confusion between the new cartridge and used cartridge as evidenced by the Afrezza Usability Test, during which two participants misidentified a used cartridge as new, and three participants misidentified a new cartridge as used.

21. Decrease the prominence of the statement "Rx Only" as this statement is as prominent as the proprietary and established names and strength.

Gen2 Inhaler Packaging Design and Label

22. Revise the label of the mouthpiece to include a statement "this side up" to improve patient comprehension that the mouthpiece should always be held in the upright position; thus, reducing a potential for dosing errors. Although the IFU specifies that the inhaler should be held with the mouthpiece in an upright position after a cartridge is loaded, eight participants in the Afrezza Usability Test held the inhaler incorrectly, which could have caused medication loss. Additionally, on 12 occasions, 5 participants held the inhaler upside down. Moreover, several participants commented that it is difficult to know which side is the top of the inhaler because it is not labeled.

23. Revise the label on the inhaler to add a statement "replace Inhaler after 15 days of use" to emphasize that the inhaler needs to be replaced on the 16th day in order to avoid dosing medication errors because this information is easy to forget.

24. Consider using a word "top" on the top part of the mouthpiece cover and using a different color for ease of use. Three participants commented that they experienced difficulty replacing the mouthpiece cover correctly.

Gen2 Inhaler Carton Labeling

25. Decrease the prominence of the phrase "Inhaler" as this phrase is not a part of the proprietary name; and thus, should be in smaller font.

26. Place the established name under the proprietary name in accordance with 21 CFR 201.10 (g)(1).

Cartridge and Gen2 Inhaler Carton Labeling

27. See Comments 16 and 22 which also apply to this Section.

28. Add a prominently displayed, bolded Medication Guide statement to the principal display panel in accordance with 21 CFR 208.24. Include one of the following statements: "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" on the principle display panel of the container labels and carton labeling. Use the first sentence ("enclosed") if the Medication Guide will be inside the carton/container and the entire carton/container is considered a unit-of-use bottle that is dispensed to a single patient. Use the second sentence ("accompanying") if the Medication Guide is glued to the container/carton, as a tear-off sheet, etc.

29. Include the route of administration "For Oral Inhalation Only" in accordance with 21 CFR 201.100(b).

We reserve additional comments on your proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated March 12, 2010, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) will be necessary for Afrezza (insulin human [rDNA] origin) inhalation powder, if it is approved, to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease.

We acknowledge the receipt of your proposed REMS included in your initial NDA submission and amended on January 8 and June 29, 2010. The proposed REMS, as amended, contains a Medication Guide and a timetable for submission of assessments of the REMS. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022472 **COMPLETE RESPONSE**

MannKind Corporation
Attention: Patricia R. Mayer, Ph.D.
Vice President Liaison, Worldwide Regulatory Affairs
61 South Paramus Road
Paramus, NJ 07652

Dear Dr. Mayer:

Please refer to your new drug application (NDA) dated and received March 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler.

We acknowledge receipt of your amendments dated March 31 (2), April 2 (2), June 4, 15, and 17, July 16, 22, and 30, August 13, 14, and 26, September 1, 11, 18, 25, and 28, and 29, October 5, 9, 12, 23, and 30, November 16 and 24 (2), December 1 (2), 4 (2), 7, 8, 11, 15 (2), and 22 (2), 2009, and January 8, 19 (2), 25, 26 (2), 27, and February 19, 2010.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues. We strongly recommend that you request an End-of-Review meeting to discuss your approach for resolving these deficiencies.

CLINICAL

1. Your NDA contained four phase 3 trials, one conducted in patients with type 1 diabetes mellitus and three conducted in patients with type 2 diabetes. An important limitation of these trials is that there was inadequate titration of insulin doses in the treatment arms for both Afrezza and comparator. Based on our analyses, only one of these four trials (Study 102, the comparison of Afrezza to NovoLog Mix 70/30 in patients with type 2 diabetes) met its primary objective for efficacy. Afrezza failed to demonstrate non-inferiority to comparators in two trials, Studies 014 and 009. In Study 103, Afrezza failed to demonstrate superiority to the comparator. More notable was the finding of statistical inferiority of Afrezza to comparators in Studies 014 and 009. These findings call into question the clinical utility of your product to treat diabetes in an era where glycemic control has been well-established to reduce long-term complications of microvascular disease in both type 1 and 2 diabetes.

Your complete response should include a detailed discussion on how currently available clinical data support the utility of Afrezza in the marketplace and clarify why additional clinical studies are not necessary.

CLINICAL PHARMACOLOGY

2. The pivotal bioequivalence study results are not reliable based on the inspection results from the Division of Scientific Investigations (DSI). Because of unreliable data from this study, the comparability of the to-be-marketed device (Model D inhaler) to the device used in your pivotal clinical trials (Model C inhaler) is not known. Choose from the following two options to address this issue:

   Option 1: Re-analyze the serum samples for insulin and glucose and address the following deficiencies identified by DSI:

   (b) (4)

   Option 2: Conduct a new pivotal bioequivalence study comparing the Model D and Model C inhalers.

3. (b) (4)

   Your complete response should address this concern.

LABELING

4. The submitted labels and labeling do not reflect the final strength of insulin, 15 units or 30 units per cartridge. The 15 unit cartridge delivers the equivalent of approximately 4

units of subcutaneous insulin and the 30 unit cartridge delivers the equivalent of approximately 8 units of subcutaneous insulin. Therefore, prescribers and patients will need to calculate how many cartridges are needed to administer a prescribed dose, which will be titrated based on patient response. Because of the differences between the labeled strength and the approximated subcutaneous insulin dose, confusion can result when prescribing, dispensing, or administering the Afrezza cartridges as patients and their providers are accustomed to working with units of subcutaneous insulin. The Afrezza labels and labeling do not reflect the final strength of insulin (15 units or 30 units per cartridge) and do not clearly state that the 15 unit cartridge delivers the equivalent of 4 subcutaneous units of insulin (b) (4) and that the 30 unit cartridge delivers the equivalent of 8 subcutaneous units of insulin (b) (4). Because of the design of the Afrezza inhaler (Model D), it is critical that this information be clearly presented on all labels and labeling to decrease the potential for confusion and medication error. Your complete response should address this concern.

5. Afrezza cartridge

   A. The Afrezza cartridge, as the immediate label of the product, should meet the requirements of 201.10(i). Although there are space limitations, the cartridge must bear the product name (Afrezza) in addition to the strength and lot number for safety and identification reasons.

   B. Remove (b) (4) from the cartridge, if possible. Because the cartridges are individually labeled with the strength and proprietary name, the (b) (4) is confusing and is no longer necessary to differentiate between the two cartridge strengths.

6. Foil Pouch Labels and Carton Labeling

   A. To ensure the foil pouch labeling is in accordance with 12 CFR 201.55, the label should display a "see package insert for dosing information" statement.

   B. Update the storage information on the foil pouch label and carton label so that it matches the storage information in the package insert labeling. Specifically, that the pouches may be stored at room temperature for up to (b) (4).

   C. (b) (4)

   D. Remove the (b) (4) Because the cartridges are individually labeled with the strength and proprietary name, the (b) (4) is confusing and is no longer necessary to differentiate between the two cartridge strengths.

7. We reserve additional comments on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content

of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

DEVICE

8. From observations based on the investigation of returned inhalers, clinical coordinator reports and a questionnaire regarding the inhaler used in your clinical trials, the Model C inhaler was redesigned to address usability concerns and mechanical robustness (e.g., (b) (4) However, the usability of the new device (the Model D inhaler) and the corresponding instructions for use that you intend to market have not been validated. It is unclear whether the modifications made to the Model C inhaler and the associated patient labeling mitigate the usability concerns and risks associated with the inhaler. Therefore, you should conduct a Human Factors evaluation (i.e., a systematic evaluation of use-related risks in the context of the overall device risk management) with a full validation study to assess the useability of the final Model D inhaler that you intend to market. For this study, you should provide a detailed description of the intended user population, use environment, user interfaces, and anticipated user interaction with the proposed device. You should also provide an evaluation of use-related risk in the context of overall risk management of the device and mitigation strategies that the user may have taken to reduce the risks associated with the proposed device. The study should address the following specific concerns with the Model D inhaler:

(b) (4)

We recommend that you submit this study protocol for review prior to conducting the study. The study should validate that the final product along with the associated patient labeling has fully met the needs of the intended users and has demonstrated safety and effectiveness in the hands of intended users. During this validation phase, at least 15 representative users should perform real tasks using a device in simulated high-risk use scenarios and in a realistic use environment. During this validation, we recommend you evaluate how the users can utilize the device safely and correctly according to the instructions for use. User performance measures may also include the type and number of errors, time required to do tasks, requests for help, accuracy, success/failure on individual task and overall performance.

For additional guidance on Medical Device Use-Safety and Human Factors, please refer to FDA guidance available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf.

9. Although there are *in vitro* data for the Model D inhaler and clinical data for the Model C inhaler, there are no data from clinical trials to support the proposed 1-year in-use life of the device. Your complete response should address this concern. Note that 1 year is a long duration of use for an inhalation device, with most devices for other pulmonary products discarded after 1 month of use.

10. The acceptance criteria/specification ranges for the following design verification tests are significantly broader than the actual test results. For future testing, tighten the acceptance criteria/specification ranges for these tests to better reflect the actual test results you have achieved.

(b) (4)

FACILITY INSPECTIONS

We have not yet completed our inspection of one of the manufacturing or testing facilities listed in the NDA. Satisfactory inspection reports for all facilities must be received before this application may be approved.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

We have determined that a REMS will be necessary for Afrezza (insulin human [rDNA] origin) inhalation powder, if it is approved, to ensure that the benefits of the drug outweigh the risks of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease, the risk of pulmonary function decline over time, and the potential risk of harm due to use by inappropriate patient populations, i.e., smokers and patients with chronic lung disease. The REMS once approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS included in your initial NDA submission and amended on January 8, 2010.

We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
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3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANNKIND CORP	Afrezza (insulin) inhalation powder

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
03/12/2010